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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,824	10/19/2005	Lynne Rainen	P-5729	7737

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EXAMINER	
UNDERDAHL, THANE E	
ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,824	RAINEN ET AL.	
	Examiner	Art Unit	
	Thane Underdahl	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,13-20 and 22-76* is/are pending in the application.

4a) Of the above claim(s) *28-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13-20 and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/18/08 (3)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 7/3/08 to claims 1, 3, 4, and 16 have been entered. Claims 2, 12, and 21 have been cancelled. No claims have been added. Claims 1, 3-11, 13-20, and 22-76 remain pending in the current application, of which claims 1, 3-11, 13-20, and 22-27 ONLY are being considered on their merits. Claims 28-76 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-11, 13-20, and 22-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an apparatus comprising a caspase inhibitor that stabilizes a collected sample to some degree against apoptosis and related effects when said sample contacts the caspase inhibitor within the apparatus, does not reasonably provide enablement for an apparatus that stabilizes any sample to any given degree in any given respect immediately upon its entering the apparatus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are currently broadly drawn to a tube that comprises a caspase inhibitor somewhere within its reservoir, said reservoir being useful for collecting a sample. The claims require that “immediately on collection” that the cells or sample (see indefiniteness rejection below) be “stabilize[d]," a requirement that is not supported by the specification or the contemporaneous art. These limitations require only that the sample enter the tube, not that they mix with the stabilizing agent to any degree; therefore, they include embodiments wherein the mere movement of a sample into an enclosed space stabilizes it against, e.g., ionizing radiation or extremely high heat. The specification does not support a claim to such a broad degree of stabilization.

Paragraphs 19-22, 36, 38, and 79-81 of the as-filed specification discuss the stabilizing agent/caspase inhibitor. The scope of the “stabilization” discussed in the disclosure is limited to “prevent[ion] or eliminat[ion] … of morphological changes, cell membrane degradation, DNA fragmentation, or loss of cell function or viability” (paragraph 20), or “inhibit[ion] or prevent[ion] of apoptosis” (paragraph 36).

Furthermore, the specification's guidance is limited to embodiments in which the sample is physically mixed with the stabilizing agent (paragraphs 21 and 22). It is noted that the specification appears to include no working examples in which any sample is stabilized in any way using any caspase inhibitor.

This rejection might be overcome by a narrowing of the claims such that the manner of stabilization is limited to those envisaged by the specification and reasonably predicted by the art; and such that the sample and the stabilizing agent physically contact each other.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-11, 13-20, and 22-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to an apparatus for collecting a "biological sample," said apparatus comprising caspase inhibitor "in an amount sufficient to stabilize cells," which is confusing. The claim does not require that the sample necessarily comprise cells (many biological samples, including urine and saliva, do not necessarily contain cells), and the relationship between the cells being stabilized and the sample being collected is not particularly pointed out. Clarification is required.

The nature of the "stabilization" is not particularly pointed out in the claim or the specification. It is not clear whether the apparatus must simply physically stabilize the

cells (i.e., contain them) or whether some chemical or biological process is being promoted or discouraged by the components of the apparatus. Clarification is required.

Even if the claim particularly required that the sample comprises cells, the claim would remain indefinite. The claim requires including a caspase inhibitor "in an amount sufficient to stabilize cells," but the specification provides insufficient guidance that the person of ordinary skill in the art could determine such an amount for each and every type of possible stabilization without undue experimentation. The proper test for determining "an effective amount" is whether or not one skilled in the art could determine specific values for the amount based on the disclosure. See *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975) and M.P.E.P. § 2173.05(c). The situation here is similar; the specification provides no guidance for identifying an amount of caspase inhibitor that is sufficient to, e.g., stabilize white blood cells in the presence of high heat, stabilize skin cells in the presence of high levels of chaotropic agents, or stabilize sperm cells in the presence of ionizing radiation. Clarification is required.

Finally, claim 1 has been amended to incorporate the limitations of canceled claim 21, i.e. that the tube be "at least partially evacuated." The examiner found this phrase to be indefinite because it is not clear what is being evacuated from the tube. Applicant alleges that the specification provides clarification (Reply, page 10). These arguments have been fully considered, but they are not persuasive. The portions of the specification referenced by applicant are exemplary and discuss only preferential embodiments. The specification includes no definition that properly limits "evacuation" to "removal of air to any degree." Therefore, the term "evacuate" must be given its plain

meaning (see M.P.E.P. § 2111.01), i.e., “to remove the contents of; to discharge” (see definition from Merriam-Webster OnLine dictionary; reference U). The examiner maintains that the claim does not particularly point out what is "partially evacuated” from the tube, given the plain definition of the term. Phrases like “**another aspect** of the present invention," “**preferably**,” and “for evacuated collection tubes, a … plug is **generally** employed” are all optional and exemplary language, not a limiting definition. If applicant means for the tube to contain an amount of air that results in a reduced internal pressure relative to atmospheric pressure, the claims should so recite.

Because claims 3-11, 13-20, and 22-27 depend from indefinite claim 1 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-7, 10, 11, and 20 remain rejected under 35 U.S.C. 102(b) as being anticipated by Charlton (1998, U.S. Patent 5,786,227) taken in light of Wilhelm et al. (1997, *Immunology Letters* 59: 53-59). This rejection addresses those embodiments in which the sample being collected is physically contacted with the caspase inhibitor in the tube.

Charlton teaches an apparatus for biological sample collection that comprises two tubes, one inside the other (Figure 5 and Abstract, e.g.). The inner tube in the apparatus of Charlton has a membrane (i.e. a mechanical separating element) that is partially coated with sodium azide (column 5, lines 5-10). The sodium azide is contained within the tube in dry form (column 4, lines 35-36). The tube has a cap to seal the first end (see reference numeral 30 at Figures 6 and 7). Charlton teaches that when a sample is collected in the outer tube and the inner tube is subsequently inserted, the sample transfers from the outer tube through the filter into the inner tube (column 4, lines 10-14); therefore, the outer tube is “evacuated" in that the sample moves from it into the inner tube. Wilhelm is cited solely as evidence that sodium azide is a caspase inhibitor (page 57, column 2).

Regarding the rejection of record, applicant alleges that Charlton does not teach a system in which the internal pressure is less than atmospheric pressure (Reply, page 12, paragraph 3). These arguments have been fully considered, but they are not persuasive. As discussed in the indefiniteness rejections, the claims do not clearly and definitely require that the pressure within the tube be any particular pressure. All that is required, given the plain definition of “evacuated,” is that something be removed from the tube. For this reason, Charlton anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-7, 10, 11, 13-20, and 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Charlton (1998, U.S. Patent 5,786,227) taken in view of Keana et al. (2001, U.S. Patent 6,184,210) and Wilhelm et al. (1997, *Immunology Letters* 59: 53-59).

Charlton teaches an apparatus for biological sample collection that comprises two tubes, one inside the other (Figure 5 and Abstract, e.g.). The inner tube in the apparatus of Charlton has a membrane (i.e. a mechanical separating element) that is partially coated with sodium azide (column 5, lines 5-10). The sodium azide is contained within the tube in dry form (column 4, lines 35-36). The tube has a cap to seal the first end (see reference numeral 30 at Figures 6 and 7). Charlton teaches that when a sample is collected in the outer tube and the inner tube is subsequently inserted, the sample transfers from the outer tube through the filter into the inner tube (column 4,

lines 10-14); therefore, the outer tube is “evacuated" in that the sample moves from it into the inner tube. Wilhelm is cited solely as evidence that sodium azide is a caspase inhibitor (page 57, column 2).

Charlton does not teach an embodiment in which the apparatus comprises two or more caspase inhibitors. Charlton does not teach an embodiment in which the stabilizing agent is lyophilized or comprises heparin or the components in claims 15-19.

Keana teaches that compositions comprising caspase inhibitors can further comprise antioxidants (column 13, lines 45-50), anticoagulants (EDTA; Example 23), buffering agents, or reducing agents (HEPES or glutathione; Example 23).

M.P.E.P. § 2144.06 states, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose .... [T]he idea of combining them flows logically from their having been individually taught in the prior art." It is therefore prima facie obvious to one of ordinary skill in the art to include multiple caspase inhibitors in the apparatus of Charlton.

Charlton teaches that the sodium azide in their separation component is dry but not that it is lyophilized. However, one of ordinary skill in the art would recognize that the simply having dried sodium azide is close enough to having lyophilized azide since the chemical properties would predictably be similar and thus obvious (M.P.E.P. § 2144.09).

Charlton teaches that their apparatus is for handling biological samples such as blood (col 1, lines 28-30). It would have been obvious to someone skilled in the art to

add a known anticoagulant such as EDTA, citrate, or heparin to the tube of the apparatus since this is a known technique to improve the storage of blood (KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007)).

A person of ordinary skill in the art would have had a reasonable expectation of success in combining the components of Keana with the caspase inhibitor in the apparatus of Charlton because Keana teaches that these components are compatible with caspase inhibitors. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Charlton, Keana, and Wilhelm as applied to claims 1, 3-7, 10, 11, 13-20, and 22-27 above, and further in view of Degen et al. (1998, U.S. Patent 5,788,862).

The teachings of Charlton, Keana, and Wilhelm are relied upon as above.

These references do not teach an embodiment in which the stabilizing member is a gel that is physically separate from the stabilizing agent.

Degen teaches an apparatus in which the membrane filter is a gel (column 8, lines 10-15) and can also be used to filter blood (column 12, lines 5-8).

Since both filters taught by Degen et al. and Charlton can be used to.filter blood, it would have been obvious to someone skilled in the art that this is the simple substitution of known membranes used for the same purpose and will predictably achieve the same result (KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007)).

Regarding the separation of the stabilizing member and the stabilizing agent, Charlton teach that the azide is there to mix with the biological sample. One of ordinary skill in the art would recognize that the azide would have the same effect if added to the tube itself and not integrated to the filter, since the chemical properties of the azide would remain unchanged. The act of making components of an apparatus integral or separable are matters of obvious engineering choice by the inventors (M.P.E.P. § 2144.04 V).

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Response to Arguments

Applicant makes the same arguments regarding the pressure within the apparatus of Charlton that were set forth against the anticipation rejection (Reply, page 15); for the reasons set forth above, these arguments are unpersuasive.

Regarding the withdrawn art rejections of record, applicant alleges that the cited art does not address the allegedly unexpected result that applicant's invention blocks the process by which "cell apoptosis on collection occurs immediately and to a very significant degree" (Reply, page 14). These arguments have been fully considered, but they are not persuasive. It is noted first that the claims are limited to an apparatus, not to any method of using the same. Second, as discussed in the indefiniteness rejection, the manner or degree of stabilization is not particularly set forth in the claims.

Finally, applicant has provided no evidence of any unexpected results regarding any effect the claimed apparatus has on any sample. This argument is merely the

argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration. As noted above, there are no working examples in the specification to support applicant's allegation of unexpected results of any kind.

No claims are allowed. No claims are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached Monday through Thursday, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Thane Underdahl
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/Lora E Barnhart/
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